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Vesicular rash in a 5-year-old boy with dyspnoea

Pęcherzykowa wysypka u 5-letniego chłopca z duszością

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Abstract

Mucocutaneous complications, including erythema multiforme, Stevens–Johnson syndrome or toxic epidermal necrolysis, may develop in up to one third of patients infected with *Mycoplasma pneumoniae*. This paper reports the case of a 5-year-old boy presenting with atypically severe pneumonia caused by *M. pneumoniae*. Cutaneous and mucosal manifestations associated with the condition were helpful in the establishment of correct diagnosis. Target (bull's-eye) lesions with possible bullae formation, as well as prominent mucosal lesions in a child accompanying features of respiratory tract infection should raise the suspicion of atypical infection.

Keywords: community-acquired pneumonia (CAP), respiratory tract infections, atypical respiratory pathogen, vasculitis, mucositis, diagnosis

Streszczenie

Powikłania skórno-śluzówkowe, obejmujące m.in. rumień wielopostaciowy, zespół Stevensa–Johnsona czy toksyczną nekrolizę naskórka, mogą się rozwinąć nawet u jednej trzeciej chorych zakażonych *Mycoplasma pneumoniae*. W niniejszej pracy przedstawiono przypadek 5-letniego chłopca, u którego zapalenie płuc o etiologii *M. pneumoniae* miało nietypowo ciężki przebieg, natomiast towarzyszące objawy skórno-śluzówkowe pozwoliły ustalić właściwe rozpoznanie. Wykwity typu „tarczy strzelniczej", z możliwym rozwojem pęcherzy, a także nasilone zmiany w obrębie śluzówek u dziecka z cechami infekcji dróg oddechowych powinny nasuwać podejrzenie zakażenia atypowego.

Słowa kluczowe: pozaszpitalne zapalenie płuc, zakażenia układu oddechowego, atypowy patogen, zapalenie naczyń, zapalenie błon śluzowych, rozpoznanie

INTRODUCTION

Mycoplasma pneumoniae, a small bacterium lacking a cell wall, the smallest of free-living bacteria, and *Chlamydophila pneumoniae*, an obligate intracellular parasite, are the most important pathogens responsible for the development of atypical pneumonia (informally referred to as walking pneumonia) – a disease with a mild, self-limiting course accompanied by low fever, chronic dry cough and good general condition of the patient. Approximately every 4–7 years, *M. pneumoniae* sets off epidemics attributed to the loss of population immunity and the development of new serotypes[1]. During epidemic seasons the microorganism may be responsible for up to 40% of pneumonia cases in children >5 years of age[2], but between epidemics infections are uncommon. In Poland, *M. pneumoniae* infection is confirmed serologically on average in 6.5% of patients under 18 years of age hospitalised for pneumonia – far less frequently than suspected[3]. The infection spreads mainly by droplet transmission, with an incubation period of 1 to 3 weeks (average 20–23 days)[4]. Even though *M. pneumoniae* infections are usually asymptomatic or mild, occasionally they may run a severe course manifested with dyspnoea, pronounced weakness and high fever, or be complicated by superinfection, e.g. *Streptococcus pneumoniae*[2].

Complications of *M. pneumoniae* infection may involve the lungs (exacerbation of coexisting pulmonary diseases, e.g. asthma, chronic obstructive pulmonary disease, rare diffuse alveolar haemorrhage syndrome) and, because of autoimmunity, all extrapulmonary organs. Major complications are known to affect the nervous system (meningitis, encephalitis, myelitis, polyradicalulopathy, Guillain–Barré syndrome, peripheral neuropathy), cardiovascular system (myocarditis, pericarditis, arrhythmias), kidneys (tubular necrosis, interstitial nephritis, glomerulonephritis), gastrointestinal tract and – relatively common in children – mucocutaneous lesions (erythema nodosum, erythema multiforme, leukocytoclastic vasculitis).

Severe or complicated course of *M. pneumoniae* infection is particularly frequently observed in children with asplenia, sickle cell anaemia, Down's syndrome and other immunocompromised conditions. The paper presents the case of a boy with mycoplasma infection complicated by mucocutaneous lesions.

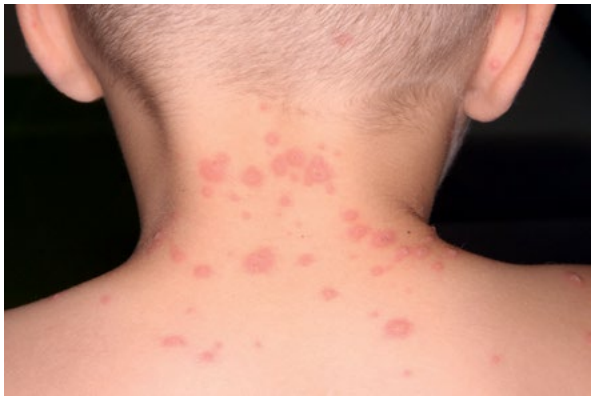

Fig. 1. Classic target lesions on the nape of the neck

CASE REPORT

A generally healthy 5-year-old boy was admitted to hospital with fever, cough and rash. The patient's parents reported that 4 days before hospitalisation the boy developed fever (up to 39.8°C), and on the following day he started coughing. On the third day of the disease, vesicular lesions appeared on the skin of the upper limbs, and on the following day they extended to the entire upper limbs and neck, also involving the vermilion border. The boy became apathetic, and refused to eat or drink. The patient's past medical history revealed chickenpox and herpes labialis. No developmental abnormalities and allergies were found, and the boy's social and travel history was unremarkable. The child's mother had a concurrent respiratory tract infection with persistent dry cough. The patient's general condition upon admission was moderately good. Notable findings were dyspnoea with faster than normal respiratory rate (up to 40 breaths/min) and reduced blood saturation (90%). Multiple annular erythematous eruptions resembling the shooting target (bull's-eye) or consisting of two distinct zones with bullae on erythematous base were observed on the skin of the face, neck, chest, buttocks, and upper and lower limbs (Figs. 1–3). The skin eruptions were particularly prominent on the elbows and knees, and in locations affected by minor injuries on the lower limbs (Köbner phenomenon) (Fig. 4). The lesions were accompanied by significant oedema, vesicular eruptions as well as erosions and crusting on the vermilion border (Fig. 5). In addition, erosions and patches of white-grey membrane covering the oral mucous membranes were noted, together with mucosal reddening and swelling in the nasal cavities, symptoms of conjunctivitis, and an extensive erosion on the glans penis. Furthermore, physical examination revealed oedema of hands and feet, and diffuse crackles over the left lung.

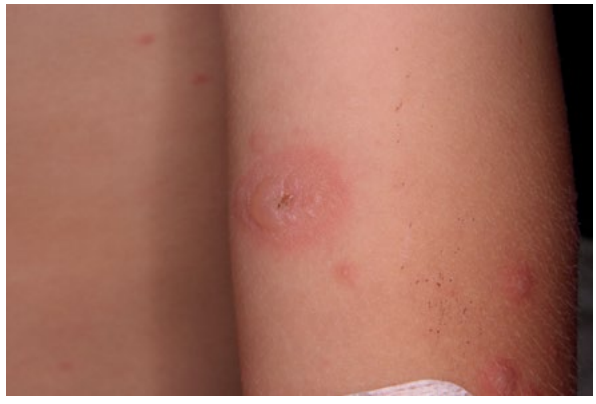

Fig. 2. Large skin eruption on the left arm, with visible central necrosis, zone of oedema, and outer ring of erythema

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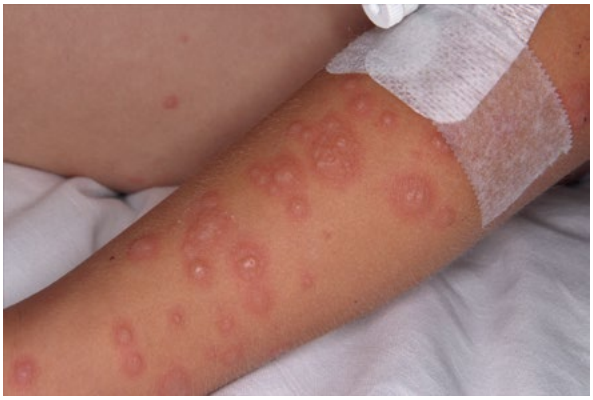

Fig. 3. Multiple vesicles on erythematous base located on the left forearm

Additional examinations demonstrated mildly elevated inflammation markers [white blood cells (WBC) 12,000/μL, C-reactive protein (CRP) 40 mg/L], while chest radiograph (CXR) demonstrated interstitial densities in the left lung (Fig. 6).

Treatment with clarithromycin, prednisone and acyclovir (because of history of recurrent herpes) was initiated. During subsequent days of hospital care, the boy's general condition was found to improve. Dyspnoea resolved rapidly, and skin lesions gradually cleared. *M. pneumoniae* infection was confirmed by serological tests (seroconversion: negative tests for specific IgG and IgM antibodies on day 4 became positive on day 11 of the disease), and by polymerase chain reaction (PCR) – positive throat swab culture.

DISCUSSION

Extrapulmonary complications of *M. pneumoniae* infection usually have an autoimmune basis because of the similarity of microbial adhesins and glycoproteins to human antigens, though direct invasion of tissues, including the skin, is also possible[2,4]. Mucocutaneous lesions are probably the most common complication of *M. pneumoniae* infections

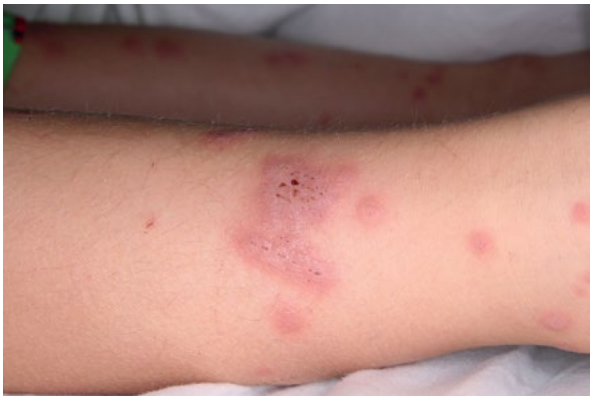

Fig. 4. Köbner phenomenon – coalescing skin lesions at injury sites (visible old scabs)

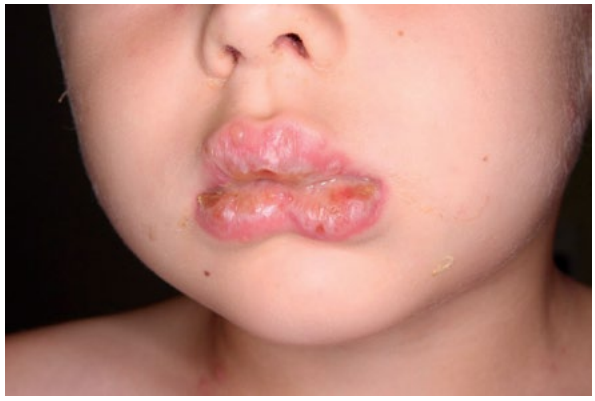

Fig. 5. Oedema and coalescing vesicles within the vermilion border

in children. Their total prevalence may reach 25–33%[5]. Based on the presence of typical target (bull's-eye) lesions in the reported patient, the diagnosis of erythema multiforme (EM) was made. EM is a self-limiting inflammatory disorder of the skin arising in the mechanism of delayed hypersensitivity reaction type IV. EM usually follows an infection (90%), but may also be related to exposure to drugs (sulphonamides, barbiturates, ibuprofen), chemical agents (benzoates, pesticides), physical factors (radiotherapy), or accompany diseases of autoaggression[6]. Among infectious agents, the herpes simplex virus (HSV) is considered to be the most prevalent, responsible for approximately 70% of EM cases in adults. In contrast, non-specific viral infections and *M. pneumoniae* predominate in children[7,8].

EM lesions are distributed symmetrically. Initially, they involve the extensor surfaces of the limbs including the palms and plantar aspects of the feet. Another characteristic feature is Köbner phenomenon, i.e. the development of lesions

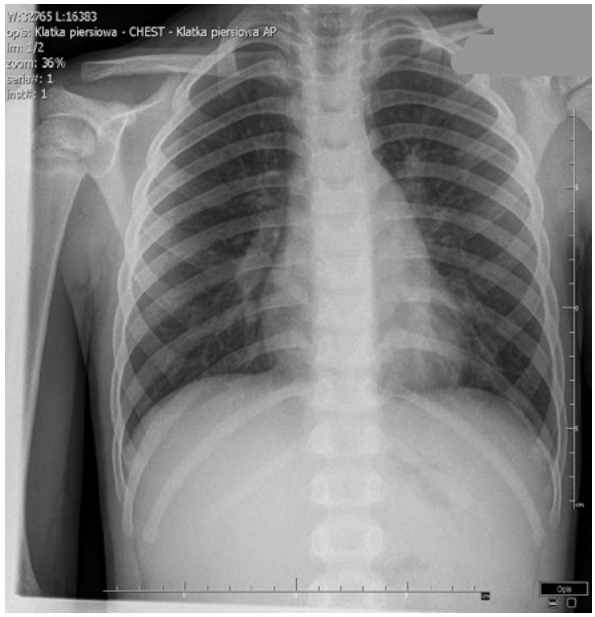

Fig. 6. CXR; interstitial densities in the left lung

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at the sites of mechanical trauma or areas of exposure to ultraviolet (UV) light. Initial erythematous-oedematous eruptions evolve into characteristic target (bull's-eye) lesions. A typical lesion has a diameter of <3 cm, and it is circular in shape, with well-delimited borders. It consists of three distinct zones: a dusky area of central necrosis, a middle zone of pale oedema, and an outer ring of erythema. In the centre and on the periphery of lesions, bullae may form which rupture easily, leading to painful erosions. The skin lesions may coalesce over time. Occasionally, in addition to three-zone lesions, atypical two-zone targets with a less well-defined border can be seen. EM occurs in two forms: minor and major. The minor form is associated with a milder course, and occurs much more commonly. EM major is characterised by a more severe course and mucosal involvement[8]. Until recently, EM was recognised as a mild form of hypersensitivity reaction, part of the same disease spectrum as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). At present, in view of different aetiology, distinct pathophysiological background and clinical picture, EM is regarded as a separate disease entity[9]. Morphologically, EM is characterised by raised target lesions, while SJS manifests as flat, often two-zone lesions, occasionally with petechiae, and with the formation of bullae and erosions, affecting no more than 10% of body surface area. Epidermal detachment associated with TEN involves more than 30% of total body surface area, while cases with detachment of 10–30% are termed as SJS/TEN overlap. The differential diagnostic process including EM, SJS and TEN is summarised in Tab. 1. EM is often mistaken for urticaria multiforme[8], a disorder characterised by eruptions (bullae) visibly raised above the skin surface, arranged in a rosette pattern, or polycyclic lesions often resembling a shooting target (bull's-eye). A characteristic feature of urticaria multiforme is rapid development and recession of skin lesions. Skin eruptions typically do not persist in the same locations for more than 24 hours. They are accompanied by oedema of the feet and hands, and often dermographism[8].

Erythema multiforme, minor form (EM minor)
- Epidermal detachment <10% of total body surface area
- Peripherally located typical target lesions (diameter <3 cm, circular, with three zones of colour change and a clearly marginated outline) and/or atypical raised lesions (diameter <3 cm, circular, with two zones of colour change and a poorly defined border)
- No mucosal involvement

Erythema multiforme, major form (EM major)
- The same as in EM minor + involvement of at least one mucosal area

Stevens–Johnson syndrome (SJS)
- Epidermal detachment <10% of total body surface area
- Flat skin lesions (round, non-palpable, with two colour zones and/or ill-defined borders)

Toxic epidermal necrolysis (TEN, Lyell syndrome)
- Epidermal detachment >30% of total body surface area
- Flat atypical lesions or spreading patches

Tab. 1. Summary of the differential diagnostic process involving EM, SJS and TEN

As mentioned, EM is a common complication of *M. pneumoniae* infection. The above aetiology of the disease in the reported patient was confirmed by accompanying symptoms of pneumonia including dry cough, dyspnoea, fever, diffuse crackles over the left lung, and interstitial lesions visible on CXR.

Serological tests for *M. pneumoniae* infection should be performed not earlier than on the 7th or 8th day after the appearance of symptoms when IgM class antibodies arise, peaking in the 2nd/3rd week of the disease. The titre of IgG antibodies rises approximately 2 weeks later[2,4]. Early identification of *M. pneumoniae* infection is possible by PCR. Compared to serological tests, the sensitivity of this method is 73–92%, and specificity 96–100%[10]. However, it should be noted that the detection of *M. pneumoniae* genetic material is not tantamount to the identification of the agent causing the current infection, as the carriage of *M. pneumoniae* may persist for a number of months after being infected. For this reason as well as technical difficulties (costs of substrate, time considerations) the culture of *M. pneumoniae* has not been integrated into routine clinical practice[2,11]. Atkinson and Waites suggest that the diagnostic work-up in *M. pneumoniae* infections in children should optimally include the evaluation of IgM and IgA, and PCR[4].

A 2016 Canadian study evaluated the frequency of *M. pneumoniae* infection in children with EM and SJS. *M. pneumoniae* was shown to be responsible for 14% cases of SJS, 22% cases of EM minor and as much as 61% cases of EM major. Distinct features of patients with EM resulting from this infection included older age, accompanying sore throat, and the presence of lesions with central bullae[12].

In 2015, Canavan et al. proposed a new disease entity – *M. pneumoniae*-induced mucocutaneous disease, also referred to as *M. pneumoniae*-induced rash and mucositis (MIRM)[13]. In the opinion of the cited authors, this is justified by unique features of the condition, such clear predominance of mucosal over cutaneous lesions, milder course compared to SJS or TEN, distinct pathomechanism associated with the presence of *M. pneumoniae* in skin lesions and – most importantly – probably a different optimal treatment regime than in SJS/TEN.

The diagnostic criteria of MIRM proposed by Canavan et al. are listed in Tab. 2. Since that publication there have been numerous reports of MIRM cases in children.

Epidermal detachment	<10%
Number of inflamed mucosal areas	At least 2
Few bullous eruptions and scattered target lesions	Yes
Features of atypical pneumonia: • **Clinical findings** • **Laboratory findings**	 Fever, coughing, positive auscultatory findings Positive IgM antibody titre, positive culture or PCR for *M. pneumoniae*, positive cold agglutinin test result

Tab. 2. Diagnostic criteria of MIRM

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In addition, the authors distinguished the following forms of the disease: "MIRM sine rash" with absent or mild cutaneous symptoms, and "severe MIRM" characterised by diffuse bullae and flat atypical target lesions.
Mucosal lesions are most typically located in the oral cavity (94%), on the conjunctiva (82%), and in the genital area (63%). Multiple skin lesions occur only in a small percentage of patients (19%). Morphologically, the skin manifestations present as vesicles or target lesions; they are usually diffuse and located on the extremities[13]. A particularly important aspect is that the prognosis in MIRM is very favourable, and therapeutic management is usually limited to antibiotic treatment targeted against *M. pneumoniae*, alleviation of symptoms, and patient hydration. There are no data on the efficacy of immunosuppressive treatment (steroid therapy or intravenous immunoglobulins), and this treatment modality is reserved for particularly severe cases.

CONCLUSIONS

Mucocutaneous lesions are among common complications of infection induced by *M. pneumoniae* in children. In patients with respiratory tract infection accompanied by mucosal involvement, especially target (bull's-eye) lesions, *M. pneumoniae* infection should be considered in differential diagnosis, and macrolides should be used in empirical therapy.

Conflict of interest

The authors do not declare any financial or personal links with other persons or organisations that might adversely affect the content of the publication or claim any right to the publication.

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